Journal of Applied Analysis and Computation
Volume 13, Number 5, October 2023, 2703–2719
Website:http://www.jaac-online.com
DOI:10.11948/20220553

OPTIMAL CONTROL OF TUMOR-LYMPHATIC MODEL WITH IMMUNO-CHEMOTHERAPY

Jingnan Wang[1,†] and Li Xu

Abstract To find optimal methods to inhibit tumors, we propose a tumor-lymphocyte immune optimal model with immuno-chemotherapy. Firstly, we investigate the therapeutic effects of high-dose single immunotherapy and high-dose single chemotherapy for tumor logistic growth, respectively. Furthermore, we apply the optimal control theory to investigate the optimal control problem of immuno-chemotherapy to eliminate tumors, maximize the remaining number of lymphocytes and minimize the cost caused by drugs over a finite time interval. The necessary and sufficient conditions for the existence of optimal control are also discussed. Finally, the numerical results indicate that the effect of immuno-chemotherapy with strong killing rate to tumors and weak killing rate to immune cells is the most effective strategy in inhibiting tumor growth.

Keywords Tumor-lymphatic model, immuno-chemotherapy, optimal control, stability.

MSC(2010) 34H05, 92B05.

1. Introduction

Cancer is a public health problem and one of the major diseases that cause people to die. In recent years, although a lot of research has been devoted to curing cancer, the treatment of cancer is still one of the most challenging problems of modern medicine [20]. Traditionally, the strategies used to treat tumors include surgery, radiotherapy and chemotherapy, but they all have side effects, and there exists the probability of tumor relapse [13]. Nowadays, evidence suggests that the immune system plays a crucial role in suppressing and eliminating tumors [1], thus many medical workers pay attention to immunotherapy [9, 16, 24], but the effect of immunotherapy on inhibiting some malignant tumors is low. Therefore, many scholars begin to study how to combine surgical treatment, radiotherapy, chemotherapy and immunotherapy organically to design more effective personalized cancer treatment strategies [3, 14, 22, 23]. Recently, scholars have established many mathematical models to explore the optimal dose, the optimal course of treatment and the minimum cost of drugs used in the course of immuno-chemotherapy [4, 5, 17, 21].

†The corresponding author.
[1]Department of applied mathematics, Harbin University of Science and technology, Harbin, 150080, China
Email: wangjingnan@hrbust.edu.cn(J. Wang), xuli_0220@163.com(L. Xu)

Referring to the optimal control methods for tumor-immune model in [17], we discuss a similar optimal control problem in the tumor-lymphocyte immune process under the combined effect of immunotherapy and chemotherapy. Considering different growth characteristics of different tumors [11], we improve the model proposed by Pang et al. in [18] with the background that the growth of lymphoma tumors [10] and colorectal tumors [8] is of Logistic type, and the specific modified model is given by

$$\begin{cases} \dfrac{\mathrm{d}L_1}{\mathrm{d}t} = \mu - r_1 L_1 + \alpha_1 \dfrac{TL_2}{\eta + T} - \beta_1(1 - e^{-C})L_1, \\ \dfrac{\mathrm{d}L_2}{\mathrm{d}t} = r_1 L_1 - \alpha_3 L_2 - \beta_2(1 - e^{-C})L_2 + \tilde{u}, \\ \dfrac{\mathrm{d}T}{\mathrm{d}t} = r_2 T(1 - \dfrac{T}{K}) - \alpha_2 T L_2 - \beta_3(1 - e^{-C})T, \\ \dfrac{\mathrm{d}C}{\mathrm{d}t} = \tilde{v} - \sigma C, \end{cases} \tag{1.1}$$

satisfying the following initial conditions

$$L_1(0) = L_{10} \geq 0, L_2(0) = L_{20} \geq 0, T(0) = T_0 \geq 0, C(0) = C_0 \geq 0, \tag{1.2}$$

where L_1, L_2 and T denote the number of immature lymphocytes, mature lymphocytes and tumor cells, respectively. C denotes the blood drug concentration. μ is the fixed rate of young lymphocytes generated by hematopoietic model in the absence of tumors, r_1 is the transformation rate from the immature lymphocytes to the mature lymphocytes, α_1 is the maximum recruitment rate of mature lymphocytes. α_3 is the inactivation rate of the mature lymphocytes, $\tilde{u}$ is the infusion dose of mature lymphocytes with anti-tumour activity. r_2 is the growth rate of tumors, α_2 is the rate of tumor cells killed by mature lymphocytes. $\beta_i(1 - e^{-C})(i = 1, 2, 3)$ indicates the fractional killing rate for the same quantity of drug C, β_1, β_2 and β_3 are the maximum killing rate of chemotherapy drugs on immature lymphocytes, mature lymphocytes and tumor cells, respectively. $\tilde{v}$ is the increment of blood drug concentration due to chemotherapy, σ is the attenuation rate of chemotherapy drugs.

The rest of this paper is organized as follows. In Sect.2, we discuss the basic properties of solutions of the model and the stability conditions of the tumor-free equilibrium (in the absence of immunotherapy or chemotherapy). In Sect.3, we consider an optimal control problem of combination therapy for anti-tumor. The necessary and sufficient conditions for the existence of optimal control are also discussed. In Sect.4, we apply numerical simulation to compare the efficacy of single immunotherapy, single chemotherapy and combination therapy, and characterize an optimal combined treatment strategy. Finally, the conclusions of the paper are given in Sect.5.

2. Qualitative analysis of the model

2.1. Non-negativity and boundedness of the solutions

Theorem 2.1. *For any $t \geq 0$, every solution of model (1.1) with initial condition (1.2) remains positive and bounded through out the region $\mathbb{R}^4_+ = \{(L_1, L_2, T, C) : L_1, L_2, T, C \in \mathbb{R}_+\}$.*

Proof. For any $t \geq 0$, from the first equation of model (1.1), we have

$$\frac{\mathrm{d}L_1}{\mathrm{d}t} \geq -[r_1 + \beta_1(1 - e^{-C})]L_1. \tag{2.1}$$

Solving equation (2.1), we obtain

$$L_1(t) \geq L_1(0) \exp\{-\int_0^t [r_1 + \beta_1(1 - e^{-C(\theta)})]\mathrm{d}\theta\} > 0.$$

Similarly, we have

$$L_2(t) \geq L_2(0) \exp\{-\int_0^t [\alpha_3 + \beta_2(1 - e^{-C(\theta)})]\mathrm{d}\theta\} > 0.$$

From the third equation of model (1.1), we have

$$\frac{\mathrm{d}T}{\mathrm{d}t} = [r_2(1 - \frac{T}{K}) - \alpha_2 L_2 - \beta_3(1 - e^{-C})]T,$$

then

$$T(t) = T(0) \exp\{\int_0^t [r_2(1 - \frac{T(\theta)}{K}) - \alpha_2 L_2(\theta) - \beta_3(1 - e^{-C(\theta)})]\mathrm{d}\theta\} \geq 0.$$

From the fourth equation of model (1.1), we obtain

$$C(t) = \frac{\tilde{v}}{\sigma} + [C(0) - \frac{\tilde{v}}{\sigma}]e^{-\sigma t} \geq 0. \tag{2.2}$$

Therefore, $L_1(t) \geq 0, L_2(t) \geq 0, T(t) \geq 0, C(t) \geq 0$ for any $t \geq 0$.

Furthermore, from (2.2), we have

$$C(t) \leq \max\{C(0), \frac{\tilde{v}}{\sigma}\}.$$

Denote $M = 1 - e^{-C} \geq 0$, from the third equation of model (1.1), we obtain

$$\begin{aligned}
\frac{\mathrm{d}T}{\mathrm{d}t} &= r_2 T - \frac{r_2}{K}T^2 - \alpha_2 T L_2 - \beta_3 M T \\
&= -\frac{r_2}{K}(T - \frac{K}{2})^2 + \frac{r_2 K}{4} - (\alpha_2 L_2 + \beta_3 M)T \\
&\leq \frac{r_2 K}{4} - (\alpha_2 L_2 + \beta_3 M)T.
\end{aligned}$$

Since $L_2(t) \geq 0$ and $T(t) \geq 0$, we have

$$\frac{\mathrm{d}T}{\mathrm{d}t} \leq \frac{r_2 K}{4} - \beta_3 M T,$$

which yields to

$$T(t) \leq N \triangleq \max\{T(0), \frac{r_2 K}{4\beta_3 M}\}.$$

In a similar way, the equations for $L_1(t)$ and $L_2(t)$ give

$$\begin{aligned}\frac{\mathrm{d}(L_1+L_2)}{\mathrm{d}t} &= \mu+\tilde{u}+\alpha_1\frac{TL_2}{\eta+T}-\beta_1 ML_1-\alpha_3 L_2-\beta_2 ML_2\\ &\le \mu+\tilde{u}-\beta_1 ML_1-(\alpha_3+\beta_2 M-\frac{\alpha_1 N}{\eta+N})L_2\\ &\le \mu+\tilde{u}-A(L_1+L_2).\end{aligned}$$

Thus,

$$L_1(t)+L_2(t)\le \max\{L_1(0)+L_2(0),\frac{\mu+\tilde{u}}{A}\},$$

where $A=\min\{\beta_1 M,\alpha_3+\beta_2 M-\frac{\alpha_1 N}{\eta+N}\}$. Hence for any $t\ge 0$, every solution of model (1.1) with initial condition (1.2) remains positive and bounded in the region $\mathbb{R}^4_+$. This completes the proof. □

2.2. Stability of tumor-free equilibrium

Referring to the optimal control methods for tumor-immune model in [17], we first discuss the efficacy of single immunotherapy and single chemotherapy.

Suppose model (1.1) only involves immunotherapy, then model (1.1) is equivalent to the following model

$$\begin{cases}\dfrac{\mathrm{d}L_1}{\mathrm{d}t}=\mu-r_1L_1+\alpha_1\dfrac{TL_2}{\eta+T},\\ \dfrac{\mathrm{d}L_2}{\mathrm{d}t}=r_1L_1-\alpha_3L_2+\tilde{u},\\ \dfrac{\mathrm{d}T}{\mathrm{d}t}=r_2T(1-\dfrac{T}{K})-\alpha_2TL_2.\end{cases}\tag{2.3}$$

Theorem 2.2. *For single immunotherapy, the tumor-free equilibrium* $E_0^*=(\frac{\mu}{r_1},\frac{\mu+\tilde{u}}{\alpha_3},0)$ *of model* (2.3) *is locally asymptotically stable for* $\tilde{u}>u_c$ *and unstable for* $\tilde{u}\le u_c$, *where*

$$u_c\doteq\frac{\alpha_3 r_2}{\alpha_2}-\mu.\tag{2.4}$$

Proof. Clearly, model (2.3) has a tumor free equilibrium $E_0^*=(\frac{\mu}{r_1},\frac{\mu+\tilde{u}}{\alpha_3},0)$, and the corresponding Jacobian matrix is

$$J(E_0^*)=\begin{pmatrix}-r_1 & 0 & \frac{\alpha_1(\mu+\tilde{u})}{\eta\alpha_3}\\ r_1 & -\alpha_3 & 0\\ 0 & 0 & r_2-\frac{\alpha_2(\mu+\tilde{u})}{\alpha_3}\end{pmatrix}$$

then the characteristic equation of model (2.3) at E_0^* is

$$(\lambda+r_1)(\lambda+\alpha_3)(\lambda-r_2+\frac{\alpha_2(\mu+\tilde{u})}{\alpha_3})=0\tag{2.5}$$

and the eigenvalues of (2.5) are given by $\lambda_1=-r_1<0$, $\lambda_2=-\alpha_3<0$ and $\lambda_3=r_2-\frac{(\mu+\tilde{u})\alpha_2}{\alpha_3}$. Therefore, when $\tilde{u}>\frac{\alpha_3 r_2}{\alpha_2}-\mu\doteq u_c$, $\lambda_3<0$. According to the Routh-Hurwitz criterion, E_0^* is locally asymptotically stable. This completes the proof. □

Remark 2.1. μ is always less than $\frac{\alpha_3 r_2}{\alpha_2}$, i.e., $u_c > 0$ in Theorem 2.2.

Suppose model (1.1) only involves chemotherapy. Then model (1.1) is equivalent to the following model

$$\begin{cases} \dfrac{\mathrm{d}L_1}{\mathrm{d}t} = \mu - r_1 L_1 + \alpha_1 \dfrac{TL_2}{\eta + T} - \beta_1(1 - e^{-C})L_1, \\ \dfrac{\mathrm{d}L_2}{\mathrm{d}t} = r_1 L_1 - \alpha_3 L_2 - \beta_2(1 - e^{-C})L_2, \\ \dfrac{\mathrm{d}T}{\mathrm{d}t} = r_2 T(1 - \dfrac{T}{K}) - \alpha_2 T L_2 - \beta_3(1 - e^{-C})T, \\ \dfrac{\mathrm{d}C}{\mathrm{d}t} = \tilde{v} - \sigma C. \end{cases} \tag{2.6}$$

Theorem 2.3. *For single chemotherapy, the tumor-free equilibrium* $E_*^0 = (\frac{\mu}{r_1+\beta_1\Theta}, \frac{r_1\mu}{(r_1+\beta_1\Theta)(\alpha_3+\beta_2\Theta)}, 0, \frac{\tilde{v}}{\sigma})$ *of model* (2.6) *is locally asymptotically stable for* $\tilde{v} > v_c$ *and unstable for* $\tilde{v} \le v_c$, *where*

$$v_c \doteq -\sigma \ln(1 - \tilde{\Theta}), \Theta = 1 - e^{-\frac{\tilde{v}}{\sigma}} \tag{2.7}$$

and

$$\tilde{\Theta} = \sqrt[3]{-\frac{Q}{2} + \sqrt{\Delta}} + \sqrt[3]{-\frac{Q}{2} - \sqrt{\Delta}} - \frac{b}{3a} \tag{2.8}$$

where

$$\Delta = (\frac{Q}{2})^2 + (\frac{P}{3})^3,\ P = \frac{c}{a} - \frac{b^2}{3a^2},\ Q = 2(\frac{b}{3a})^2 - \frac{bc}{3a^2} + \frac{d}{a}.$$

Proof. It is easy to know that model (2.6) has a tumor-free equilibrium $E_*^0 = (L_1^*, L_2^*, T^*, C^*) = (\frac{\mu}{r_1+\beta_1\Theta}, \frac{r_1\mu}{(r_1+\beta_1\Theta)(\alpha_3+\beta_2\Theta)}, 0, \frac{\tilde{v}}{\sigma})$, and the corresponding Jacobian matrix is

$$J(E_*^0) = \begin{pmatrix} -r_1 - \beta_1\Theta & 0 & \frac{\alpha_1 L_2^*}{\eta} & -\beta_1 L_1^* e^{-\frac{\tilde{v}}{\sigma}} \\ r_1 & -\alpha_3 - \beta_2\Theta & 0 & -\beta_2 L_2^* e^{-\frac{\tilde{v}}{\sigma}} \\ 0 & 0 & r_2 - \alpha_2 L_2^* - \beta_3\Theta & 0 \\ 0 & 0 & 0 & -\sigma \end{pmatrix}$$

then the characteristic equation of model (2.6) at E_*^0 is

$$(\lambda + r_1 + \beta_1\Theta)(\lambda + \alpha_3 + \beta_2\Theta)(\lambda - r_2 + \alpha_2 L_2^* + \beta_3\Theta)(\lambda + \sigma) = 0 \tag{2.9}$$

and the eigenvalues of (2.9) are given by $\lambda_1 = -(r_1+\beta_1\Theta) < 0$, $\lambda_2 = -(\alpha_3+\beta_2\Theta) < 0$, $\lambda_3 = -\sigma < 0$ and $\lambda_4 = r_2 - \alpha_2 L_2^* - \beta_3\Theta$.

Denote

$$F(\Theta) = (r_1 + \beta_1\Theta)(\alpha_3 + \beta_2\Theta)(-r_2 + \alpha_2 L_2^* + \beta_3\Theta) = a\Theta^3 + b\Theta^2 + c\Theta + d,$$

where

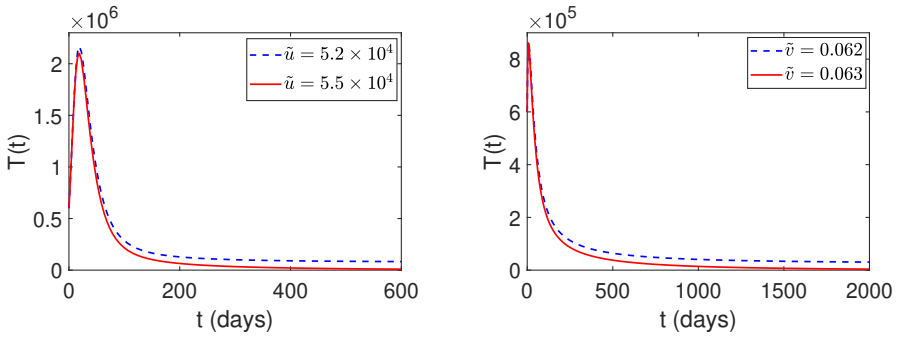
$$a = \beta_1\beta_2\beta_3, b = r_1\beta_2\beta_3 + \alpha_3\beta_1\beta_3 - r_2\beta_1\beta_2,$$
$$c = r_1\alpha_3\beta_3 - r_1 r_2\beta_2 - \alpha_3 r_2\beta_1, d = \alpha_2 r_1\mu - \alpha_3 r_1 r_2.$$

By the Kaldan formula, the cubic equation $F(\Theta) = 0$ has a positive root

$$\tilde{\Theta} = \sqrt[3]{-\frac{Q}{2} + \sqrt{\Delta}} + \sqrt[3]{-\frac{Q}{2} - \sqrt{\Delta}} - \frac{b}{3a}.$$

Therefore, when $\tilde{v} > v_c$, $(1 - e^{\frac{\tilde{v}}{\sigma}}) > \tilde{\Theta}$. Then $F(\Theta) > 0$, which reveals $\lambda_4 < 0$. According to the Routh-Hurwitz criterion, E_*^0 is asymptotically stable. This completes the proof. □

Remark 2.2. The $\tilde{\Theta}$ shown in Eq.(2.8) is always in the interval $(0, 1)$, i.e., $v_c > 0$ in Theorem 2.3.



(a) Single immunotherapy (b) Single chemotherapy

Figure 1. The variations of the number of tumors with time for single therapy.

Based on the estimated values of every parameter in Table 1, we have $u_c = 5.3857 \times 10^4$ and $v_c = 0.0625$. Taking $\tilde{u} = 5.5 \times 10^4 > u_c$ and $\tilde{v} = 0.063 > v_c$, we know that high-dose single immunotherapy and single chemotherapy need 600 days and 2000 days to eliminate the tumor with size 6×10^5 respectively, and the tumor cannot be eliminated when $\tilde{u} = 5.2 \times 10^4 < u_c$ or $\tilde{v} = 0.062 < v_c$ (as shown in Fig.1). That is, both high-dose single immunotherapy and single chemotherapy can wipe out tumors eventually, but it needs a long time. Therefore, in order to alleviate the pain of patients and prolong their survival time, we will next consider the anti-tumor effect of chemotherapy combined with immunotherapy, and seek an optimal combined treatment strategy.

3. The optimal control problem

Since the dimensions of u_c and v_c are not consistent, referring to the optimal control methods for tumor-immune model in [17], we make the following transformation for

model (1.1): $L_1 = x_1, L_2 = u_c x_2, T = y, C = v_c z$, then a new model is given by

$$\begin{cases} \dfrac{\mathrm{d}x_1}{\mathrm{d}t} = \mu - r_1 x_1 + \alpha_4 \dfrac{x_2 y}{\eta + y} - \beta_1 (1 - e^{-v_c z}) x_1, \\ \dfrac{\mathrm{d}x_2}{\mathrm{d}t} = r_3 x_1 - \alpha_3 x_2 - \beta_2 (1 - e^{-v_c z}) x_2 + u, \\ \dfrac{\mathrm{d}y}{\mathrm{d}t} = r_2 y (1 - \dfrac{y}{K}) - \alpha_5 x_2 y - \beta_3 (1 - e^{-v_c z}) y, \\ \dfrac{\mathrm{d}z}{\mathrm{d}t} = v - \sigma z, \end{cases} \tag{3.1}$$

where $\alpha_4 = \alpha_1 u_c,\ r_3 = \frac{r_1}{u_c},\ \alpha_5 = \alpha_2 u_c,\ u = \frac{\tilde{u}}{u_c},\ v = \frac{\tilde{v}}{v_c}$.

From Theorem 2.2 and Theorem 2.3, the number of tumors will eventually reach zero if and only if $u > 1$ or $v > 1$ for model (3.1). Based on the above analysis, we take u and v as control variables and limit them in $[0, 1]$. Recording the state variables and control variables of model (3.1) as $O(t) = [x_1(t), x_2(t), y(t), z(t)]^{\mathrm{T}}$ and $w(t) = [u(t), v(t)]^{\mathrm{T}}$, then model (3.1) can be written as

$$O'(t) = f(t, O(t), w(t)), t \in [0, t_f]. \tag{3.2}$$

In addition, the concentration of chemotherapy drugs in patients should not exceed the maximum tolerable concentration z_{max}, otherwise it will produce toxicity [15]. Thus, model (3.1) has a constraint condition

$$0 \le z(t) \le z_{\max}. \tag{3.3}$$

In [17], Pang et al. minimized the number of tumor cells as well as the costs produced by immunotherapy and chemotherapy. Our aim is to design a combination therapy strategy to minimize the number of tumors, the number of killing lymphocytes and the cost of combination therapy as much as possible. Thus, the cost function is defined as

$$J(u(t), v(t)) = \varepsilon_1 y(t_f) - \varepsilon_2 x_1(t_f) - \varepsilon_3 x_2(t_f) + \int_0^{t_f} [\frac{1}{2}(\varepsilon_u u^2(t) + \varepsilon_v v^2(t))]\mathrm{d}t, \tag{3.4}$$

where the linear function $[\varepsilon_1 y(t_f) - \varepsilon_2 x_1(t_f) - \varepsilon_3 x_2(t_f)]$ (denoted by $\Phi[t_f, O(t_f)]$ ($[t_f, O(t_f)] \in S \subset \mathbb{R}^5_+$)) is used to evaluate the killing degree of tumors, immature lymphocytes and mature lymphocytes after treatment, ε_1, ε_2 and ε_3 are the weight factors related to the number of tumors, immature lymphocytes and mature lymphocytes, respectively. The quadratic function $\frac{1}{2}[\varepsilon_u u^2(t) + \varepsilon_v v^2(t)]$ (denoted by $L[t, w(t)]$) represents the cost of immunotherapy and chemotherapy, ε_u and ε_v are weight factors related to the cost of immunotherapy and chemotherapy, respectively. Thus, the optimal problem can be transformed into seeking an optimal control pair (u^*, v^*) such that

$$J(u^*, v^*) = \min\{J(u, v) : u, v \in V\}, \tag{3.5}$$

where V is the admissible control set and defined as

$$V = \{\, (u(t), v(t)) |\, (u(t), v(t)) \in L^\infty([0, t_f], \mathbb{R}^2_+), u(t), v(t) \in [0, 1]\}. \tag{3.6}$$

3.1. Existence of optimal control

To prove the existence of optimal solutions for equation (3.4), we use Theorem 4.1 given by Fleming and Rishel in [7] and Theorem 9.2.1 given by Lukes in [12].

Theorem 3.1. *There exists an optimal solution* $(O^*, u^*, v^*) \in V^{1,\infty}([0, t_f], \mathbb{R}^4_+) \times L^\infty([0, t_f], \mathbb{R}^2_+)$ *for the optimal control problem* (3.2)-(3.4) *such that*

$$J(u^*, v^*) = \min\{J(u, v) : u, v \in V\}, \tag{3.7}$$

where $O^* = (x_1^*, x_2^*, y^*, z^*)^{\mathrm{T}}$ *and* V *is the admissible control set defined on* $[0, 1]$. *if the following conditions are satisfied:*

(i) The admissible control set V *and the corresponding variables with initial conditions are non-empty;*

(ii) The admissible control set V *is convex and closed;*

(iii) The set S *is compact and* $\Phi[t_f, O(t_f)]$ *is continuous on* S*;*

(iv) The right-hand side of the state equation (3.2) *is continuous and satisfies the Lipschitz condition with respect to the state variables. Furthermore, it is bounded by a linear combination of the state and control variables and can be written as a linear function of control variables;*

(v) The integrand $L[t, w(t)]$ *of the cost function is convex on* V *and is bounded below.*

Proof. (1) From Theorem 1.1, it is easy to see that the solutions of model (3.1) are also non-negative and bounded. Furthermore, the coefficients of model (3.1) are positive. Therefore, the state variables and control variables of V with the initial conditions are non-empty.

(2) By the definition of the control set V, it is clear that the control set V is bounded and convex.

(3) The set S is closed and bounded, thus S is compact. Obviously, $\Phi[t_f, O(t_f)]$ is continuous on S.

(4) Clearly, right-side function $f(t, O(t), w(t))$ of state equation (3.2) is continuous, and model (3.1) can be expressed as

$$f(t, O(t), w(t)) = \varpi_1 O(t) + \varpi_2(t, O(t), w(t)),$$

where

$$\varpi_1 = \begin{pmatrix} -r_1 - \beta_1 & 0 & 0 & 0 \\ r_3 & -\alpha_3 - \beta_2 & 0 & 0 \\ 0 & 0 & r_2 - \beta_3 & 0 \\ 0 & 0 & 0 & -\sigma \end{pmatrix}$$

and

$$\varpi_2(t, O(t), w(t)) = \begin{pmatrix} \mu + \alpha_4 \frac{x_2 y}{\eta + y} + \beta_1 x_1 e^{-v_c z} \\ \beta_2 x_2 e^{-v_c z} + u \\ -\frac{r_2 y^2}{K} - \alpha_5 x_2 y + \beta_3 y e^{-v_c z} \\ v \end{pmatrix}.$$

Since the state variables of model (3.1) are bounded, there is a constant $C_1 > 0$ such that

$$\left|\varpi_2(t,\bar{O}(t),w(t)) - \varpi_2(t,O(t),w(t))\right| \le C_1\left|\bar{O}(t) - O(t)\right|,$$

then we get

$$\left|f(t,\bar{O}(t),w(t)) - f(t,O(t),w(t))\right| \le C_2\left|\bar{O}(t) - O(t)\right|,$$

where $C_2 = \|\varpi_1\| + C_1$. That is, $f(t,O(t),w(t))$ satisfies the Lipschitz condition with respect to $O(t)$.

Furthermore, model (3.1) can also be expressed as

$$f(t,O(t),w(t)) = \sigma_1(t,O(t)) + \sigma_2 w(t), \tag{3.8}$$

where

$$\sigma_1(t,O(t)) = \begin{pmatrix} \mu - r_1x_1 + \alpha_4\frac{x_2y}{\eta+y} - \beta_1(1-e^{-v_cz})x_1 \\ r_3x_1 - \alpha_3x_2 - \beta_2(1-e^{-v_cz})x_2 \\ r_2y(1-\frac{y}{K}) - \alpha_5x_2y - \beta_3(1-e^{-v_cz})y \\ -\sigma z \end{pmatrix}, \quad \sigma_2 = \begin{pmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 0 \\ 0 & 1 \end{pmatrix}.$$

Since the solution of model (3.1) is bounded, there are some constants $h_1, h_2, h_3 > 0$ such that

$$\begin{aligned} |f(t,O(t),w(t))| &= |\sigma_1(t,O(t)) + \sigma_2 w(t)| \\ &\le |\sigma_1(t,O(t))| + |\sigma_2|\,|w(t)| \\ &\le h_1 + h_2\,|O(t)| + h_3\,|w(t)| \\ &\le h_0(1 + |O(t)| + |w(t)|) \end{aligned}$$

where $h_0 = \max\{h_1, h_2, h_3\}$.

(5) In order to verify the convexity of the integrand $L[t,w(t)]$ on the control set V, we need to prove that the inequality

$$L(t,(1-q)w_1 + qw_2) \le (1-q)L(t,w_1) + qL(t,w_2) \tag{3.9}$$

always holds for any $q \in (0,1)$ and $w_1 = (w_{11}, w_{12}), w_2 = (w_{21}, w_{22}) \in V$. We can easily get

$$\begin{aligned} L(t,(1-q)w_1 + qw_2) &= \sum_{i=1}^{2} \frac{\varepsilon_i[(1-q)w_{1i} + qw_{2i}]^2}{2}, \\ (1-q)L(t,w_1) + qL(t,w_2) &= \sum_{i=1}^{2} \frac{\varepsilon_i[(1-q)w_{1i}^2 + qw_{2i}^2]}{2}, \end{aligned}$$

then we have

$$\begin{aligned} &L(t,(1-q)w_1 + qw_2) - [(1-q)L(t,w_1) + qL(t,w_2)] \\ =&\sum_{i=1}^{2} \frac{\varepsilon_i}{2}[(1-q)^2w_{1i}^2 + q^2w_{2i}^2 + 2q(1-q)w_{1i}w_{2i} - (1-q)w_{1i}^2 - qw_{2i}^2] \end{aligned}$$

$$
\begin{aligned}
&= \sum_{i=1}^{2} \frac{\varepsilon_i}{2} [q(q-1)w_{1i}^2 + q(q-1)w_{2i}^2 + 2q(1-q)w_{1i}w_{2i}] \\
&= \sum_{i=1}^{2} \frac{\varepsilon_i}{2} q(q-1)(w_{1i} - w_{2i})^2
\end{aligned}
$$

and $q(q-1) \leq 0$, so equation (3.9) always holds. That is, $L[t, w(t)]$ is a convex function on the control set V.

Finally, we only need to prove that the integrand $L[t, w(t)]$ is bounded below. It is easy to obtain

$$
\begin{aligned}
L[t, w(t)] &= \frac{1}{2}[\varepsilon_u u^2(t) + \varepsilon_v v^2(t)] \geq M_1[u^2(t) + v^2(t)] \geq M_1[u^2(t) + v^2(t)] - M_2 \\
&\geq M_1 |w|^{\kappa} - M_2
\end{aligned}
$$

where $M_1 = \frac{1}{2}\min\{\varepsilon_u, \varepsilon_v\}, M_2 > 0$ and $\kappa = 2$. This completes the proof. □

3.2. Characterization of optimal control

In the previous subsection, we obtained the existence of optimal control. Now, we evaluate the necessary conditions for optimal control by using Pontryagin's Maximum Principle [19]. In order to deduce the system optimality, we have formulated the Hamiltonian function including state constraint as follows:

$$
H = \frac{1}{2}(\varepsilon_u u^2(t) + \varepsilon_v v^2(t)) + \sum_{i=1}^{4} \psi_i(t) f(t, O(t), w(t)) + \xi(t)k \tag{3.10}
$$

where

$$
\xi(t) = \begin{cases} pf, & k \geq 0 \\ 0, & k < 0 \end{cases}
$$

and $k = z(t) - z_{\max}$, pf is a penalty factor [4]. The adjoint variables $\psi_i (i = 1, 2, 3, 4)$ are the solution of the following system

$$
\begin{aligned}
\psi'_1 &= -\frac{\partial H}{\partial x_1} = \psi_1[r_1 + \beta_1(1 - e^{-v_c z})] - \psi_2 r_3, \\
\psi'_2 &= -\frac{\partial H}{\partial x_2} = -\psi_1 \frac{\alpha_4 y}{\eta + y} + \psi_2[\alpha_3 + \beta_2(1 - e^{-v_c z})] + \psi_3 \alpha_5 y, \\
\psi'_3 &= -\frac{\partial H}{\partial y} = -\psi_1 \frac{\alpha_4 \eta x_2}{(\eta + y)^2} + \psi_3[r_2(\frac{2y}{K} - 1) + \alpha_5 x_2 + \beta_3(1 - e^{-v_c z})], \\
\psi'_4 &= -\frac{\partial H}{\partial z} = (\psi_1 \beta_1 x_1 + \psi_2 \beta_2 x_2 + \psi_3 \beta_3 y) v_c e^{-v_c z} + \psi_4 \sigma - \xi(t),
\end{aligned} \tag{3.11}
$$

with transversality condition

$$
\begin{aligned}
\psi_1(t_f) &= \frac{\partial \Phi[t_f, O(t_f)]}{\partial x_1} = -\varepsilon_2, \quad \psi_2(t_f) = \frac{\partial \Phi[t_f, O(t_f)]}{\partial x_2} = -\varepsilon_3, \\
\psi_3(t_f) &= \frac{\partial \Phi[t_f, O(t_f)]}{\partial y} = \varepsilon_1, \quad \psi_4(t_f) = \frac{\partial \Phi[t_f, O(t_f)]}{\partial z} = 0,
\end{aligned} \tag{3.12}
$$

where $\Phi[t_f, O(t_f)]$ is the terminal performance index of the cost function (3.4).

Theorem 3.2. *There exists an optimal control* $(u^*, v^*) \in V$ *and optimal state* $O^* = (x_1^*, x_2^*, y^*, z^*)^{\mathrm{T}}$ *such that*

$$J(u^*, v^*) = \min\{J(u, v) : u, v \in V\},$$

then the characterization of the optimal control pair are given by

$$u^* = \max\{\min\{-\frac{\psi_2}{\varepsilon_u}, 1\}, 0\}, v^* = \max\{\min\{-\frac{\psi_4}{\varepsilon_v}, 1\}, 0\}, \tag{3.13}$$

where $\psi_i (i = 1, 2, 3, 4)$ *satisfy the adjoint equation* (3.11) *subject to the transversality conditions* (3.12).

Proof. According to the Pontryagin's Maximum Principle, the control variable (u^*, v^*) is the minimum point of the cost function $J(u, v)$ and the Hamiltonian function H. By equating to zero the derivatives of H with respect to the control variables, we obtain

$$\begin{aligned} \frac{\partial H}{\partial u} &= \varepsilon_u u^* + \psi_2 = 0, \\ \frac{\partial H}{\partial v} &= \varepsilon_v v^* + \psi_4 = 0. \end{aligned}$$

Thus we have $u^*(t) = -\frac{\psi_2}{\varepsilon_u}, v^*(t) = -\frac{\psi_4}{\varepsilon_v}$. Using the property of the control set, we have

$$u^*(t) = \begin{cases} 0, & \frac{\psi_2}{\varepsilon_u} \geq 0, \\ -\frac{\psi_2}{\varepsilon_u}, & \frac{\psi_2}{\varepsilon_u} \in (-1, 0), \\ 1, & \frac{\psi_2}{\varepsilon_u} \leq -1 \end{cases}$$

and

$$v^*(t) = \begin{cases} 0, & \frac{\psi_4}{\varepsilon_v} \geq 0, \\ -\frac{\psi_4}{\varepsilon_v}, & \frac{\psi_4}{\varepsilon_v} \in (-1, 0), \\ 1, & \frac{\psi_4}{\varepsilon_v} \leq -1. \end{cases}$$

This completes the proof. □

Therefore, we obtained an optimization model consisting of initial conditions, state equation (3.1), adjoint equation (3.11), transversality conditions (3.12) and

optimal control pairs (3.13) as follows:

$$\begin{cases} \dfrac{\mathrm{d}x_1^*}{\mathrm{d}t} = \mu - r_1 x_1^* + \alpha_4 \dfrac{x_2^* y^*}{\eta + y^*} - \beta_1 (1 - e^{-v_c z^*}) x_1^*, \\ \dfrac{\mathrm{d}x_2^*}{\mathrm{d}t} = r_3 x_1^* - \alpha_3 x_2^* - \beta_2 (1 - e^{-v_c z^*}) x_2^* + \max\{\min\{-\dfrac{\psi_2}{\varepsilon_u}, 1\}, 0\}, \\ \dfrac{\mathrm{d}y^*}{\mathrm{d}t} = r_2 y^* (1 - \dfrac{y^*}{K}) - \alpha_5 x_2^* y^* - \beta_3 (1 - e^{-v_c z^*}) y^*, \\ \dfrac{\mathrm{d}z^*}{\mathrm{d}t} = \max\{\min\{-\dfrac{\psi_4}{\varepsilon_v}, 1\}, 0\} - \sigma z^*, \\ x_1^*(0) = x_{10}^*, x_2^*(0) = x_{20}^*, y^*(0) = y_0^*, z^*(0) = z_0^*, \\ {\psi'}_1 = \psi_1 [r_1 + \beta_1 (1 - e^{-v_c z^*})] - \psi_2 r_3, \\ {\psi'}_2 = -\psi_1 \dfrac{\alpha_4 y^*}{\eta + y^*} + \psi_2 [\alpha_3 + \beta_2 (1 - e^{-v_c z^*})] + \psi_3 \alpha_5 y^*, \\ {\psi'}_3 = -\psi_1 \dfrac{\alpha_4 \eta x_2^*}{(\eta + y^*)^2} + \psi_3 [r_2 (\dfrac{2y^*}{K} - 1) + \alpha_5 x_2^* + \beta_3 (1 - e^{-v_c z^*})], \\ {\psi'}_4 = (\psi_1 \beta_1 x_1^* + \psi_2 \beta_2 x_2^* + \psi_3 \beta_3 y^*) v_c e^{-v_c z^*} + \psi_4 \sigma - \xi(t), \\ \psi_1(t_f) = -\varepsilon_2, \psi_2(t_f) = -\varepsilon_3, \psi_3(t_f) = \varepsilon_1, \psi_4(t_f) = 0. \end{cases} \tag{3.14}$$

4. Numerical simulations

In this section, numerical simulations are performed to illustrate the treatment effect for three different therapeutic strategies (i.e., single immunotherapy, single chemotherapy and immuno-chemotherapy). We implement the so-called forward-backward sweep method by using the scheme proposed in [2] to solve the optimality system (3.14), and to show the change states of lymphocytes and tumors in each therapeutic strategy of 100 days.

Without loss of generality, we choose the initial conditions as follows:

$$x_1(0) = 2.1 \times 10^4, x_2(0) = 70, y(0) = 6 \times 10^5, z(0) = 0$$

and the rest of the parameters of model (1.1) are given in Table 1. Meanwhile, we assumed the maximum drug concentration $z_{max} = 1.4426$, penalty factor $pf = 10000$, weight coefficient $\varepsilon_1 = 2000$, $\varepsilon_2 = 1500$, $\varepsilon_3 = 1500$, $\varepsilon_u = 500$ and $\varepsilon_v = 500$ by referring to [17]. Then the optimal states and the optimal controls corresponding to three different treatment strategies are shown in Fig.2, and the numerical results are:

$$\begin{aligned} &\textit{Single immunotherapy}: \ x_1^*(100) = 2.253 \times 10^4, x_2^*(100) = 31.03, y^*(100) = 1668, \\ &\textit{Single chemotherapy}: \ x_1^*(100) = 2.240 \times 10^4, x_2^*(100) = 5.981, y^*(100) = 84.68, \\ &\textit{Immuno} - \textit{chemotherapy}: \ x_1^*(100) = 2.246 \times 10^4, x_2^*(100) = 28.01, y^*(100) = 1.154. \end{aligned}$$

By observing the above numerical results, it can be noted that immunotherapy has the least killing effect on lymphocytes, followed by immuno-chemotherapy, and chemotherapy has the greatest killing effect on lymphocytes. Although the number of tumors is significantly reduced when the above three treatment strategies are implemented respectively, immuno-chemotherapy is the best strategy in eliminating

Table 1. Parameter descriptions and estimated values of (1.1)

Parameter: Description	Value	Source
μ: Rate of immature lymphocyte production	1.35×10^4 day^{-1}	Estimated
r_1: Maturation rate of immature lymphocytes	0.62 cells^{-1}day^{-1}	Estimated
r_2: Tumor cells growth rate	0.18 day^{-1}	[10]
K: Tumor cells carrying capacity	5×10^6 cells	[10]
α_1: Maximum mature lymphocytes recruitment rate	0.1254 day^{-1}	[10]
η: Steepness coefficient of mature lymphocytes recruitment	2.019×10^7 cells	[10]
α_2: Decay rate of tumour cells by mature lymphocytes	1.101×10^{-7} cells^{-1}day^{-1}	[10]
α_3: The inactivation rate of the mature lymphocytes	0.0412 day^{-1}	[10]
β_1: Fractional immature lymphocytes killed by chemotherapy	0.034 day^{-1}	[6]
β_2: Fractional mature lymphocytes killed by chemotherapy	0.034 day^{-1}	[6]
β_3: Fractional tumor cells killed by chemotherapy	0.9 day^{-1}	[6]
σ: Rate of chemotherapy drug decay	0.3466 day^{-1}	[17]

tumors. To further verify the effectiveness of the optimal control strategy, the efficacy of immuno-chemotherapy strategy with fixed drug dosage (i.e., u and v are equal to the initial or terminal values of the optimal control variables u^* and v^*) or optimal control (i.e., $u = u^*, v = v^*$) are compared in Fig.3, which shows that immuno-chemotherapy with optimal control is still the most effective strategy in reducing the number of inactivated lymphocytes and inhibiting tumor growth.

In order to exhibit the efficacy of optimal combination therapy clearly, we define the efficacy function as

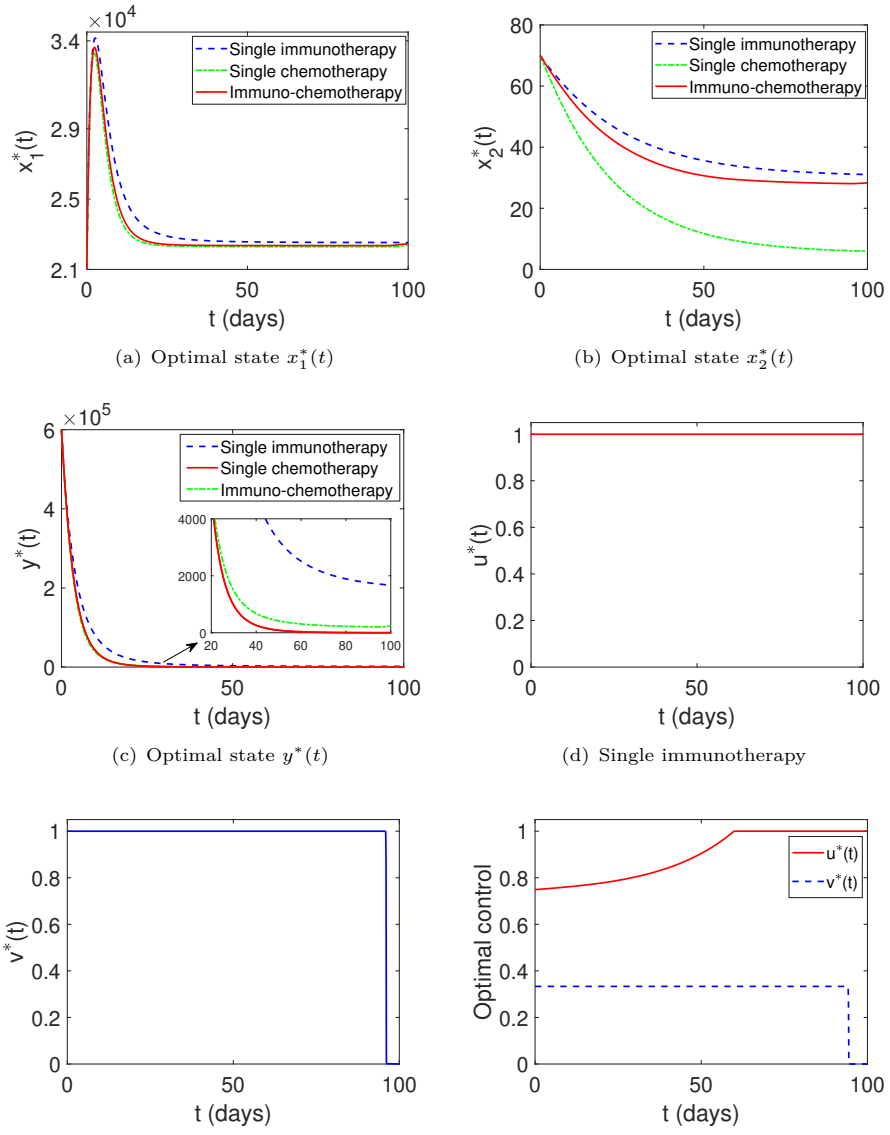
$$E(t) = \frac{y(0) - y^*(t)}{y(0)},$$

where $y(0)$ is the initial number of tumor cells, and y^* is the optimal state corresponding to optimal controls u^* and v^*. From Fig.4(b), it can be seen that the elimination rate of tumors can reach more than 99 percent after 26 days by adopting the optimal immuno-chemotherapy of $r = 0.18$.

Moreover, when the growth rate of tumor cells increases to $r = 0.39$, the drug dose of the optimal immuno-chemotherapy strategy used in the early stage changes to the combination of low-dose immunotherapy (with gradually increasing dose) and low-dose chemotherapy, and single immunotherapy is used in the post-treatment period (as shown in Fig.4(a)). Meanwhile, the elimination rate of tumors can reach 99 percent after only 8 days (as shown in Fig.4(b)). The results indicate that the inhibitory effect of drugs on tumor growth is more effective in the acute stage of cancer, but less obvious in the chronic advanced stage.

5. Conclusion

In this paper, through investigating the effects of the immuno-chemotherapy on killing tumors, we obtain that high-dose single immunotherapy and high-dose single chemotherapy are not enough to eliminate tumor cells, which means that monotherapy for tumor cells is not the best choice for patients. Using the optimization function with the minimal cost of drugs, maximal number of killing tumor cells and minimal number of killing lymphocytes, we discuss the effects of combination



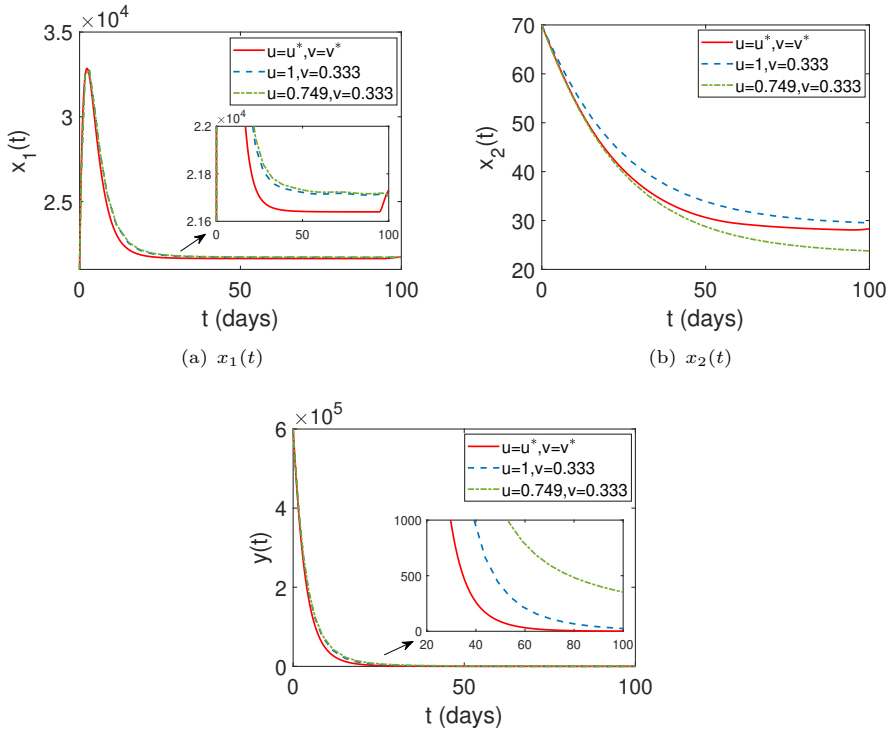
(a) Optimal state $x_1^*(t)$ (b) Optimal state $x_2^*(t)$

(c) Optimal state $y^*(t)$ (d) Single immunotherapy

(e) Single chemotherapy (f) immuno-chemotherapy

Figure 2. Time series plots of optimal states and optimal control variables of the optimality system for different therapeutic strategies.

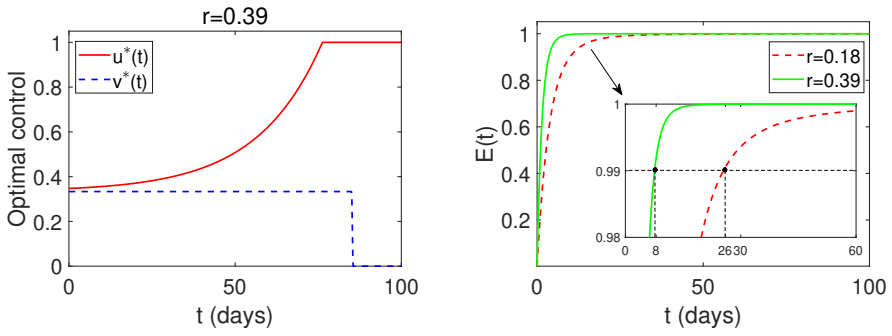
therapy by applying the optimal control theory, and obtain the optimal drug strategy to suppress the tumor growth. Numerical simulation results of three different strategies in 100 days show that the optimal immuno-chemotherapy can eliminate tumors effectively, and it is more effective in the acute stage of tumor growth. The development of new drugs with strong killing rate to tumor and weak killing rate to immune cells is an effective strategy.



(a) $x_1(t)$ (b) $x_2(t)$

(c) $y(t)$

Figure 3. Efficacy of immuno-chemotherapy for different drug doses.



(a) Optimal control variables (b) Efficacy function

Figure 4. Time series plots of optimal control variables and efficacy function for the optimal immuno-chemotherapy.

Acknowledgements

The authors would like to deeply appreciate anonymous reviewers and editors for their careful reading, insightful suggestions and comments contributed to this paper.

References

[1] F. M. Burnet, *The concept of immunological surveillance*, Prog. Exp. Tumor Res, 1970, 13, 1–27.

[2] C. Campos, J. Cristiana and D. F. M. Torres, *Numerical optimal control of HIV transmission in Octave/Matlab*, Math. Comput. Appl., 2019, 25(1), 1–20.

[3] Y. Chen and X. Lai, *Modeling the effect of gut microbiome on therapeutic efficacy of immune checkpoint inhibitors against cancer*, Math. Biosic., 2022, 350, 108868.

[4] L. G. De Pillis and A. E. Radunskaya, *A mathematical tumor model with immune resistance and drug therapy: an optimal control approach*, Comput. Math. Method M., 2001, 3(2), 79–100.

[5] P. Das, S. Das, P. Das, et al., *Optimal control strategy for cancer remission using combinatorial therapy: a mathematical model-based approach*, Chaos Soliton Fract., 2021, 145, 110789.

[6] L. G. De Pillis, W. Gu and A. E. Radunskaya, *Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations*, J. Theor. Biol., 2006, 238(4), 841–862.

[7] W. H. Fleming and R. W. Rishel, *Deterministic and Stochastic Optimal Control*, Springer-Verlag, New York, 1975.

[8] M. Grapin, C. Richard, E. Limagne, et al., *Optimized fractionated radiotherapy with anti-PD-L1 and anti-TIGIT: a promising new combination*, J. Immunother. Cancer, 2019, 7(1), 1–12.

[9] A. Hoos, *Evolution of end points for cancer immunotherapy trials*, Annals of Oncology, 2012, 23(8), 47–52.

[10] V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor, et al., *Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis*, Bull. Math. Biol., 1994, 56(2), 295–321.

[11] A. K. Laird, *Dynamics of tumor growth*, Brit. J. Cancer, 1964, 13(3), 490–502.

[12] D. L. Lukes, *Differential Equations: Classical to Controlled*, Academic Press, New York, 1982.

[13] J. Lackie, *A Dictionary of Biomedicine*, Oxford University Press, Oxford, 2010.

[14] S. Lenhart and J. T. Workman, *Optimal Control Applied to Biological Models*, Chapman and Hall/CRC, London, 2007.

[15] R. Martin and K. L. Teo, *Optimal Control of Drug Administration in Cancer Chemotherapy*, World Scientific, Singapore, 1993.

[16] H. Neves and H. F. Kwok, *Recent advances in the field of anti-cancer immunotherapy*, BBA Clinical, 2015, 3, 280–288.

[17] L. Pang, Z. Zhao and X. Song, *Cost-effectiveness analysis of optimal strategy for tumor treatment*, Chaos Soliton Fract., 2016, 87, 293–301.

[18] L. Pang, S. Liu, X. Zhang, et al., *Mathematical modeling and dynamic analysis of anti-tumor immune response*, J. Appl. Math. Comput., 2020, 62(1–2), 473–488.

[19] L. S. Potryagin, *The Mathematical Theory of Optimal Processes*, CRC Press, New York, 1987, 17–21.

[20] F. A. Rihan, S. Lakshmanan and H. Maurer, *Optimal control of tumour-immune model with time-delay and immuno-chemotherapy*, Appl. Math. Comput., 2019, 353, 147–165.

[21] G. W. Swan, *Role of optimal control theory in cancer chemotherapy*, Math. Biosci., 1990, 101(2), 237–284.

[22] Y. Wang, J. Tian and J. Wei, *Lytic cycle: a defining process in oncolytic virotherapy*, Appl. Math. Model., 2013, 37, 5962–5978.

[23] J. Wang and Y. Zhang, *Dynamics of immunotherapy antitumor models with impulsive control strategy*, Math. Meth. Appl. Sci., 2022, 45, 483–499.

[24] H. Zhang and J. Chen, *Current status and future directions of cancer immunotherapy*, J. Cancer, 2018, 9(10), 1773–1781.